Notice of Allowability	Application No.	Applicant(s)	
	08/487,312	MILLER ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *amendment filed 12/20/2004*.

2. ☒ The allowed claim(s) is/are *19,20,22,23,25,26,29,30,41 and 42*.

3. ☒ The drawings filed on *07 June 1995* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 8/8/2005
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Lorraine Spector, Ph.D.
Primary Examiner
Art Unit: 1647

The information disclosure statement submitted 8/8/2005 (as requested by the Examiner). References 7 and 14 therein have not been initialed, as they are previously of record in this application.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Kate Murashige on 8/8/2005.

The application has been amended as follows:

The claims have been amended as reflected on the attached sheets, faxed to the Examiner by Kate Murashige on 8/9/2005.

The title of the invention has been amended to read -- BOVINE GROWTH HORMONE RECOMBINANTLY PRODUCED IN E. COLI--

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

Applicants arguments in the paper filed 3/26/2004 have been fully considered. The Eppard reference (J. Endocrinology 1342:47-56, 1992) establishes that bGH that has been produced recombinantly in *E. coli* has properties significantly different from bGH purified from bovine pituitary. Although the pbGH used by Eppard was not purified by the same method as used by Daniels, the properties of the preparations as tested by Eppard should have been similar, and the *reason* for the difference between recombinantly produced and pituitary-derived bGH, the four amino acid deletion that occurs *in vivo*, as demonstrated by Eppard, would be expected to be represented in both pbGH preparations. Specifically, Eppard demonstrates that all forms of recombinant bGH with the exception of $Ala^{1}Leu^{127}$ bGH had higher biological activity *in vivo*

than did pbGH (page 50 and Table 2). Thus, Eppard establishes that there is a real qualitative difference between the claimed bGH and that of the prior art. Further, at the paragraph bridging pages 50 and 54, Eppard suggests that the reason for the lower activity of the pituitary derived protein is degradation of the protein, specifically removal of the four amino-terminal residues. This result might be expected to be duplicated if the protein were expressed recombinantly in mammalian cells, but does not occur when *E. coli* is used as the host cell. Prior to the Eppard disclosure, one of ordinary skill in the art would not have been motivated and had a reasonable expectation of success at separating the various individual forms from a pbGH preparation such as that disclosed by Daniels. To date, the art has not reported such a separation of the components of a pbGH preparation.

There are other teachings of Eppard that are relevant to other amendments and arguments presented by applicants. At page 49, Eppard states that recombinant production of delta 1-4 bGH in *E. coli* results in 80% protein that has been de-methioninylated and 20% of protein bearing an amino terminal methionine residue. At the paragraph bridging pages 50 and 54, and again at pages 54-55, Eppard teaches that the results obtained *in vivo* using lactating cows *do not* correlate to either the *in vitro* nor other *in vivo* systems that have been used to test bGH activity.

In view of the above evidence, the claims are found to be allowable. The amendments to the claims are to indicate that *E. coli* is the host cell, and additionally to delete reference to 'allelic variants', which is not found to have basis in the specification as originally filed. It is noted that in the discussion included with the requested fax transmission received 8/8/2005, that applicant has pointed out that the dimorphism in BGF at residue 127 (where either leucine or alanine may occur) has been known in the art since at least 1973.

In the submission filed 12/2004, applicants submitted three declarations that must be considered in the interest of a complete file history:

The Petersen, Bradley, and Mahla declarations under 37 CFR 1.132 filed 26 March 2004 are insufficient to overcome the rejection of claims 19-22 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being obvious over Daniels (U.S. Patent 3,265,579) for the following reasons. First, it is noted that these declarations were submitted extremely late in prosecution, after a Board decision had been rendered affirming the rejection. Nevertheless, in the interest of providing a complete prosecution history, the

declarations were not considered untimely in view of the decision on petition mailed 26 January 2004.

Second, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

The Petersen declaration under 37 CFR 1.132 filed 26 March 2004 is insufficient to overcome the rejection of claims 19-22 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being obvious over Daniels (U.S. Patent 3,265,579) for the following reasons. Dr. Petersen is an expert in the field of pathology and neuroscience, particularly as they relate to prion diseases such as mad cow disease (MCD). There is no evidence of record that he has a material interest in the outcome of this application. Regarding the nature of the fact sought to be established, Dr. Petersen declares that recombinant bovine growth hormone (rBGH) poses essentially no risk of MCD whereas pituitary bovine growth hormone (pBGH) has a high risk, if MCD is present in the population (emphasis added, see point 6). Dr. Petersen also declares that, if pituitaries in the pool used to purify pBGH were infected, then standard purification techniques (such as those used in Daniels) would not remove the infectious agent that causes MCD (emphasis added, see point 29). However, as the Board of Patent Appeals and Interferences stated in the decision mailed 26 March 2003, notwithstanding appellants' emphasis that the claimed rBGH has a warranty of freedom from the causative agent for MCD, this is something that Daniels' pBGH would also encompass. The Board did not find that the asserted warranty constitutes a patentable distinction over Daniels (see p. 19 of the Board decision). The opposing evidence is that MCD was not recognized until the mid-1980s, as acknowledged in the Petersen declaration (see point 9). Daniels was published in 1966. Therefore, the pBGH of Daniels could not have been contaminated. Furthermore, it is noted that there has not been an outbreak of MCD in this country. Use of the Daniels method in an uninfected herd of cows would not be contaminated. Finally, while Dr. Petersen states that it is

his opinion that the purification method of Daniels would fail to remove the MCD infectious agent, the statement is not made with reference to factual support. Daniels used several purification steps, including size exclusion chromatography, and achieved purification to a single peak. Declarant has not established how these steps fail to achieve purification of pBGH from the MCD infectious agent. Finally, Dr. Petersen declares that rBGH is structurally different from pBGH in that rBGH has one isoform whereas pBGH is a mixture of four allelic and splice variants (see point 29). However, this statement is also not made with reference to any factual support. For all of these reasons, the Petersen declaration was found to be insufficient to overcome the rejection.

The Bradley declaration under 37 CFR 1.132 filed 26 March 2004 is insufficient to overcome the rejection of claims 19-22 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being obvious over Daniels (U.S. Patent 3,265,579) for the following reasons. Dr. Bradley is an expert in the field of veterinary pathology, particularly as it relates to bovine spongiform encephalopathy (BSE), also known as MCD. There is no evidence of record that he has a material interest in the outcome of this application. Regarding the nature of the fact sought to be established, Dr. Bradley states that, if BSE infectivity has been present in the brain, pituitary gland, or in material that might contaminate the anterior pituitary gland, the risk of contamination would be high (see point 17). However, as discussed above, the opposing evidence of record indicates that the pBGH of Daniels, disclosed in 1966, could not have been contaminated since MCD was not observed until the mid-1980s, a fact that Dr. Bradley also attests to (see point 1). Furthermore, as discussed above, the Daniels method could not yield a contaminated pBGH if it is isolated from a herd of uninfected cows, such as those in the U.S. to date. Finally, Dr. Bradley also opines that the purification method of Daniels would fail to remove the MCD infectious agent. However, since the statement is not made with reference to factual support, it is not found to be persuasive.

The Mahla declaration under 37 CFR 1.132 filed 26 March 2004 is insufficient to overcome the rejection of claims 19-22 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being obvious over Daniels (U.S. Patent 3,265,579) for the following reasons. Dr. Mahla is an expert in the field of economics. There is no evidence of record that he has a material interest in the outcome of this application; however, it is noted that

he has served as an expert on commercial success in many patent court proceedings (see Dr. Mahla's C.V., attached to the declaration). Regarding the nature of the fact sought to be established, Dr. Mahla establishes that rBGH has enjoyed significant commercial success. The evidence to support this are generally along two lines. First, up to approximately 20% of cattle are treated with rBGH one year after its commercial introduction (see point 4a). Second, Monsanto experienced significant growth due to sales of rBGH (sold as "Posilac"). many facts are referred to in support of these points, and they are not disputed. however, their relevancy is not entirely clear. When relying upon secondary evidence of non-obviousness, the declarant must establish a nexus between the alleged merits or benefits of the claimed invention and the evidence offered. See Cable Elec. Prods., Inc. v. Genmark, Inc., 770 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985); Vandenberg v.Dairy Equip. Co., 740 F.2d 1560, 224 USPQ 195 (Fed. Cir. 1984); Simmons Fastener Corp. v. Illinois Tool Works, Inc., 739 F.2d 157, 222 USPQ 744 (Fed. Cir. 1984); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). If commercial success is the secondary evidence proffered, the evidence must be due to a claimed feature of the invention. See In re Noznick, 478 F.2d 1260, 178 USPQ 43 (CCPA 1973); Marconi Wireless Tel. Co. v. United States, 320 U.S. 1, 35 n. 20, 57 USPQ 471. In the instant case, it is clear that rBGH is used by a large number of dairy farmers. However, no evidence was set forth regarding the percentage of cows injected with other forms of BGH, such as pBGH or other forms of growth hormone. No evidence has been submitted regarding a growth in "market share." The commercial success has not been tied to the merits of the rBGH product claimed since other factors contributing to commercial success have not been addressed. These factors include price and advertising, among other factors. In view of all of these considerations, the declaration attempting to establish commercial success is not sufficient to overcome the rejection.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

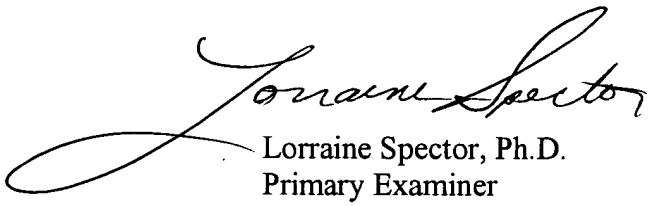
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner